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Initial Assessment of Positron Emission Tomography for Detection of Nonpalpable Regional Lymphatic Metastases in Melanoma

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Background: The purpose of this pilot study is to determine the feasibility of positron emission tomography with fluorodeoxyglucose (FDG-PET) for detection of nonpalpable regional lymph node metastases in patients with melanoma.
Methods: Adult patients with histologically proven cutaneous melanoma planned to undergo surgical lymphadenectomy for treatment of nonpalpable subclinical or residual metastatic melanoma in regional lymph node basin(s) participated. Each patient underwent attenuation-corrected PET imaging of the regional lymph node basin(s) with F18 fluorodeoxyglucose (FDG) followed by complete surgical lymphadenectomy. FDG-PET scans were interpreted prospectively by an experienced nuclear medicine physician. FDG-PET scan interpretations and histologic results were then correlated.
Results: Eleven patients underwent 12 FDG-PET scans followed by 12 operations to clear 14 regional lymph node basins. FDG-PET correctly predicted the presence of metastatic melanoma in seven of seven surgical specimens. FDG-PET scans correctly predicted the absence of disease in seven of seven histologically negative node basins. Sensitivity was 1.0; specificity was 1.0.
Conclusions: This study suggests that increased fluorodeoxyglucose uptake in palpably unremarkable regional lymph node basins in patients with melanoma is highly suggestive of metastatic disease.
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KEY WORDS: lymphadenectomy; surgery; lymph nodes; nuclear medicine; diagnostic imaging

INTRODUCTION

Melanoma is rapidly increasing in incidence in the United States [1]. By virtue of its metastic potential, melanoma accounts for the vast majority of deaths from cutaneous neoplasms.

Surgery remains the definitive therapy for melanoma. Most patients with local–regional disease can be rendered clinically disease free surgically, but many patients with deep primary lesions or regional metastases will later develop distant metastatic disease. American Joint Committee on Cancer (AJCC) stage II and III [2] patients are commonly considered for extensive regional surgical therapy, such as lymph node dissections and limb perfusion, based on a calculated probability of subclinical metastatic disease [3–6]. While elective lymph node dissection is a controversial procedure in the treatment of melanomas, retrospective studies suggest improved sur-

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vival for patients whose subclinical regional metastatic deposits are removed prior to clinical appearance [4,6–9]. Currently, regional lymph node staging is performed by clinical examination or by histologic analysis of sentinel lymph nodes or lymphadenectomy specimens. No noninvasive diagnostic test can reliably identify subclinical metastatic disease in lymph nodes.

Accurate determination of disease extent is a key prerequisite for treatment planning, both to minimize morbidity and maximize survival. Positron emission tomography (PET) has been useful in assessing metastic disease in several human tumors [10–13]. The glucose positron emitter analog 2-(F18) fluoro-2-deoxy-D-glucose (FDG) is vigorously accumulated by melanoma tumors with excellent tumor to nontumor uptake ratios, allowing visualization of metastatic deposits [14–16]. FDG-PET has recently been shown to be a sensitive imaging modality for detection of systemic metastatic melanoma in humans [17–19].

The feasibility of using FDG-PET for detection of lymph node metastases has recently been demonstrated, including the detection of subclinical metastases within normal-size lymph nodes [17]. FDG-PET might be a useful staging tool for regional lymph node basins in patients with melanoma. Because there have been no studies evaluating FDG-PET for detection of nonpalpable melanoma metastases in regional lymph node basins by histologic analysis of mapped complete lymphadenectomy specimens, false-negative and false-positive rates are unknown. The purpose of this pilot study is to determine the feasibility of FDG-PET for detection of regional lymph node metastatses in lymph node basins at high risk for harboring nonpalpable disease.

METHODS

Between September 1994 and September 1995, a prospective nonrandomized pilot study was conducted at Indiana University Medical Center and affiliated hospitals. The study protocol was approved by the Indiana University–Purdue University at Indianapolis Institutional Review Board and subjects gave written informed consent. Volunteer subjects were recruited from the patient population of the Indiana University Cancer Center Melanoma Program. Adult patients with histologically proven cutaneous melanoma planned to undergo surgical lymphadenectomy of clinically nonpalpable lymph node basin(s) believed to be at high risk for subclinical or residual metastatic melanoma were eligible for the study. Each patient underwent routine preoperative staging, including complete history and examination, chest radiography, complete blood counts, and liver function tests. Patients with intermediate-depth axial melanoma without prior wide excision underwent lymphoscintigraphy to identify the appropriate draining basin(s) for lymphadenectomy. Pre-FDG-PET scan distant metastatic disease, palpable regional lymphadenopathy, or infection of the lymph node basin were criteria for exclusion.

Prior to lymphadenectomy, each patient underwent whole body imaging with FDG-PET. Patients fasted overnight prior to the PET scan. Thirty minutes prior to imaging, patients were injected with approximately 10 millicuries (mCi) of F18 fluorodeoxy-D-glucose. Attenuation-corrected scans were obtained from the top of the shoulders to the proximal femurs at 5 min/bed position using a Siemens ECAT 951 R PET scanner (Siemens Medical Systems, Erlangen, Germany). The bladder was cleared of radioactive urine by continuous saline flushing through a triple-lumen catheter. If the primary tumor was located in the scalp, attenuation corrected views of the head were also obtained. FDG-PET images were reconstructed in the transaxial, sagittal, and coronal planes.

FDG-PET scans were interpreted prospectively by an experienced nuclear medicine physician who was provided with only the clinical diagnosis of melanoma and location of the lymph node basin(s) in question. No other clinical information or correlative studies were made available. The surgeon was blinded to the results of the regional FDG-PET scan preoperatively. Suspected findings of distant metastatic disease were communicated to the surgeon preoperatively and further evaluated with computed tomography (CT) prior to surgery.

Patients without distant disease and those without conventional imaging confirmation of abnormal distant FDG-PET findings underwent complete regional lymphadenectomy. Lymphadenectomy included, for axillary basins, removal of nodal levels I, II, and III and the supraxillary fat pad; and for inguinal basins, removal of superficial inguinal nodes only, unless metastases were identified, in which case ipsilateral iliac and obturator dissections were also performed.

Surgical specimens were fixed in formalin, sectioned, and analyzed with hematoxylin and eosin (H&E) stain. If H&E analysis revealed no melanoma in any lymph nodes, additional sections were analyzed with S-100 and HMB-45 immunohistochemical stains. The total number of nodes removed and the number and diameter of nodes found to contain metastatic melanoma were recorded.

The results of the prospective FDG-PET scan interpretations were correlated with the histological results to determine the sensitivity and specificity of FDG-PET for prediction of metastatic melanoma in the surgical specimens.

RESULTS

Twelve patients underwent imaging with FDG-PET. One patient with a negative scan refused surgery and was excluded from the study. Eleven evaluable patients (four female, seven male) underwent 12 operations for surgical clearance of 14 regional lymph node basins (10 axillary, three inguinal, and one iliac). In the 11 evaluable pa-

TABLE I. Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Pilot Study: Patient Characteristics and Results

AJCC stage[a] Primary site	Procedure	Basin(s)	No. of nodes/+nodes	Regional FDG-PET	Distant FDG-PET
1. T3aN0M0	ELND[b]	R axilla	22/0	Neg[k]	Neg
Back	ELND	L axilla	8/0	Neg	Neg
2 T3aN0M0 L thumb	ELND	L axilla	32/0	Neg	Neg
3 T3bN0M0 Axillary fold	ELND	L axilla	15/0	Neg	Neg
4 T2N0M0 L leg	ELND	R inguinal	17/0	Neg	Neg
5 T3aN1M0 Back	CLND[c]	R axilla	6/3	Neg	Neg
6 T3aN1M0 Back	CLND[d]	R axilla	3/2	Pos[l]	Left adrenal
7 T4N1M0 Back	TLND[e]	R axilla	28/5	Pos	Neg
8 T3N2bM0	CLND[f]	R inguinal	8/2	Pos	Neg
R leg	ELND	R iliac	4/0	Neg	Neg
9 T2N1M0 Back	CLND[g]	R axilla	30/5	Pos	Neg
10 T3aN2bM0	ELND[h]	L axilla	21/0	Neg	Subcutaneous nodule
Back	Resect intransit metastasis				
11 T3aN2bM0 Back	CLND[i]	L axilla	0, fat and scar negative	Neg	Neg
12 T2N2bM0 R leg	TLND[j] Limb perfusion	R inguinal	26/19	Pos	Mediastinum Left leg muscle R leg intransits

[a]AJCC, American Joint Committee on Cancer Staging System.
[b]ELND, elective lymphadenectomy (based on tumor depth).
[c]CLND, completion lymphadenectomy (of nonpalpable residual lymph node basin after excisional biopsy of solitary lymph node).
[d]FDG-PET scan revealed left adrenal uptake not confirmed on CT scan. Completion lymphadenectomy after prior open biopsy revealed two of three axillary nodes positive for melanoma. A subsequent CT scan revealed a 2-cm abnormal gland; needle biopsy confirmed metastatic melanoma.
[e]TLND, therapeutic lymphadenectomy (after positive fine-needle biopsy of equivocally palpable ''reactive'' axillary lymph node).
[f]Patient with single intransit recurrence underwent local resection and positive excisional biopsy of suspicious solitary inguinal lymph node. PET showed nonpalpable residual positive nodes. Patient underwent completion inguinal and iliac lymphadenectomy.
[g]CLND lymphadenectomy of nonpalpable axilla after complete clinical response to multiagent chemotherapy.
[h]Elective lymphadenectomy with resection of a nearby intransit metastasis. PET scan correctly predicted lymph nodes negative for tumor and correctly identified a 1.0-cm nonpalpable extra nodal metastasis.
[i]Surgical re-exploration of a previously resected lymph node basin (see scan 10) for an irregular nonpalpable persistent postoperative axillary fluid collection, detected by CT scan but negative for tumor by preoperative needle aspiration. Note: scans 10 and 11 were done on the same patient.
[j]Multiple cutaneous intransit recurrence with clinically nonpalpable inguinal lymph node basin at FDG-PET imaging. Patient developed suspicious palpable lymph nodes during 34-day interval between imaging and palliative node dissection and isolation limb perfusion.
[k]Neg, no areas of increased fluorodeoxyglucose uptake suspicious for metastatic disease were noted.
[l]Pos, one or more areas of increased (abnormal) fluorodeoxyglucose uptake suspicious for metastatic melanoma were prospectively identified.

tients, 12 preoperative FDG-PET scans were performed 1 day to 34 days prior to 12 surgical procedures. One patient was eligible for the study twice and underwent two FDG-PET scans and two surgical procedures. No FDG-PET scan-related toxicity was observed.

Patient characteristics, FDG-PET scan results, and lymphadenectomy results are presented in Table I. All lymph node basins were documented as clinically unremarkable or not suspicious for subclinical or residual metastatic disease by palpation alone prior to FDG-PET imaging. Patient 12 developed palpable regional lymph nodes during the 34-day interval between PET imaging and lymphadenectomy.

FDG-PET correctly predicted the presence of metastatic melanoma in seven of seven surgical specimens (six containing lymph node metastases, one containing a nonpalpable intransit subcutaneous nodule). The seven true-positive scans were noted in seven patients known to have AJCC stage III recurrent melanoma. FDG-PET correctly predicted the absence of disease in seven of seven lymph node basins histologically proven to be free of metastases. No false-positive or false-negative scans

were observed. Sensitivity for lymph node metastatases was 1.0; specificity was 1.0.

The mean number of lymph nodes removed per basin was 16 (range 3–32). Thirty-six lymph nodes with metastatic disease and one metastatic subcutaneous nodule were confirmed histologically in the seven specimens correctly predicted be preoperative FDG-PET scan. The median number of tumor-containing nodes per specimen was 3; the mean number was 5.3. Tumor-containing lymph nodes ranged in size from 2 mm to 2.6 cm in diameter, with a mean diameter of 1.2 cm. Metastatic deposits within these nodes were typically visible without magnification (macroscopic), ranging in size from 1.0 mm to 2.6 cm on cross section, with several nodes completely replaced by tumor. Multiple subcortical metastatic nodules were typically present within each node (Fig. 1). All metastases were demonstrated by H&E analysis. Additional sections of lymph nodes shown to be negative by H&E were analyzed, using immunohistochemical stain S-100 and HMB-45. These demonstrated no additional occult metastic foci.

PET scan demonstrated three abnormal foci suspicious for distant metastases in two patients. Patient No. 6 had a left adrenal abnormality that was not identified initially by computed tomography (CT) scan. Follow-up CT scan confirmed metastatic melanoma by CT-guided fine-needle biopsy of a 2-cm adrenal gland (Fig. 2). Patient No. 12 had two areas of abnormal FDG uptake in the mediastinum and in the deep muscle of the left leg. The left leg areas could not be confirmed clinically and were thought to represent exercised skeletal muscle. CT scan demonstrated otherwise normal-appearing 1.0- and 1.5-cm mediastinal lymph nodes.

Review of patients' records revealed six of the seven patients with true positive FDG-PET scans had prior imaging of the lymphadenectomy basins with CT and/or magnetic resonance imaging (MRI) scans. Suspicious lymphadenopathy was noted in two patients; the other four were normal. Therefore, CT/MRI identified only two of six (33%) basins containing metastatic disease correctly predicted by FDG-PET.

DISCUSSION

Accurate staging of disease extent in melanoma remains problematic. Management of patients with localized melanoma, depending on surgical philosophy, may include surgical interrogation or elective (prophylactic) lymphadenectomy of clinically normal regional lymph node basins. Elective lymph node dissection based on tumor depth is usually limited to patients with AJCC/T2 N0 M0 and T3 N0 M0 patients, with only 20–40% of patients having proven lymph node metastases at surgery [20]. This practice remains controversial, with conflicting data provided by numerous retrospective and two prospective studies [4–9,21–25].

Intraoperative lymph node mapping with selective lymphadenectomy has been described by Morton and colleagues [26,27] to more accurately stage and select patients for lymphadenectomy. While clearly an improvement over elective lymph node dissection based on tumor depth, lymphatic mapping with sentinel node biopsy has several practical drawbacks. These include its inherent invasiveness, requirement for localizing lymphoscintigraphy in most patients, and possible multiple surgical procedures. Lymph node mapping may not be reliable after prior wide excision of the primary tumor. Excellent results with selective lymphadenectomy may be difficult to produce in the hands of community surgeons who only occasionally treat melanoma.

Anatomical imaging studies such as CT and MRI scans are sensitive tests for morphologically enlarged lymph nodes and larger metastases, but are inherently insensitive for foci of tumor within normal sized lymph nodes. Several investigators have shown that CT scans of the brain, chest, abdomen, and pelvis, as well as bone scans are of no value in patients with primary melanoma [28,29]. The yield of these imaging studies is also low in patients with recurrent melanoma. Buzaid et al. [30] recently demonstrated a higher false-positive (22%) than true-positive (7%) rate in a retrospective series of 89 patients with local–regional disease. A single noninvasive test that could simultaneously assess the presence of metastatic tumor in regional and distant sites would substantially improve the staging and surveillance and provide cost effectiveness in the management of melanoma patients.

Recently, FDG-PET has been shown to be a useful staging modality in patients with metastatic melanoma. Gritters et al. [17] reported detection of metastatic melanoma in seven lymph node basins, including three cases involving normal-size lymph nodes. Six of these were confirmed by biopsy or clinical progression. Steinert et al. [18] reported 33 patients, 17 of whom had peripheral lymph node metastases on FDG-PET confirmed by correlative CT, MRI, or biopsy. Boni et al. [19] reported a series of 15 patients with known or suspected metastatic melanoma. Nine patients had peripheral lymph node FDG-PET scans, confirmed by a combination of CT, MRI, and biopsy. Two were true negative, one false negative, and seven true positive.

These studies are flawed by comparison of FDG-PET to conventional imaging techniques, which are known to be inadequate for detection of subclinical metastatic malanoma. The clinical status of imaged lymph node basins are not carefully described. Other limitations include limited or inconsistent techniques of histologic analysis and lack of lymphatic mapping to identify all basins at risk for metastatic disease. Therefore, the true false-positive and false-negative rates for FDG-PET imaging of regional lymph nodes are undefined. Compari-

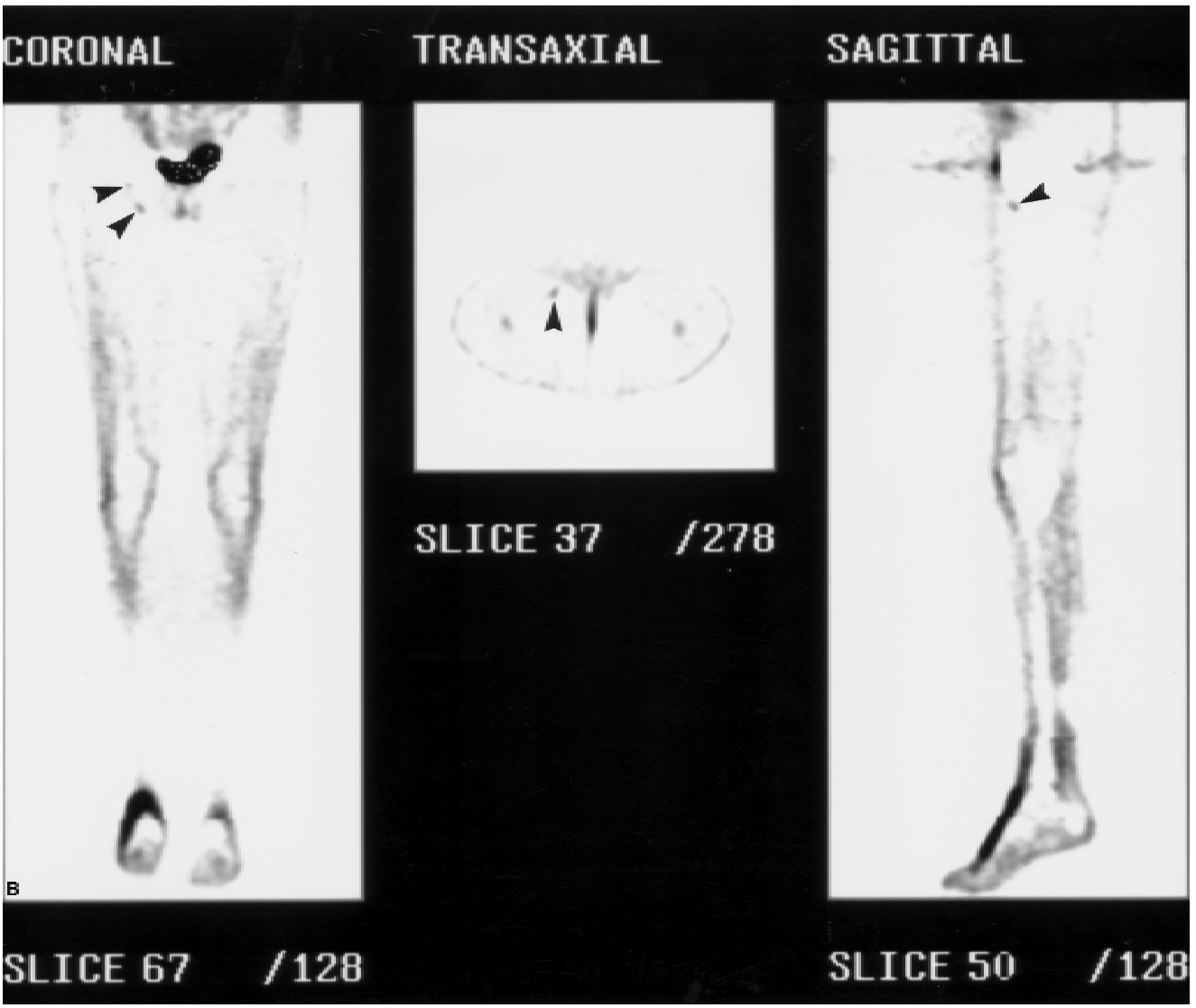
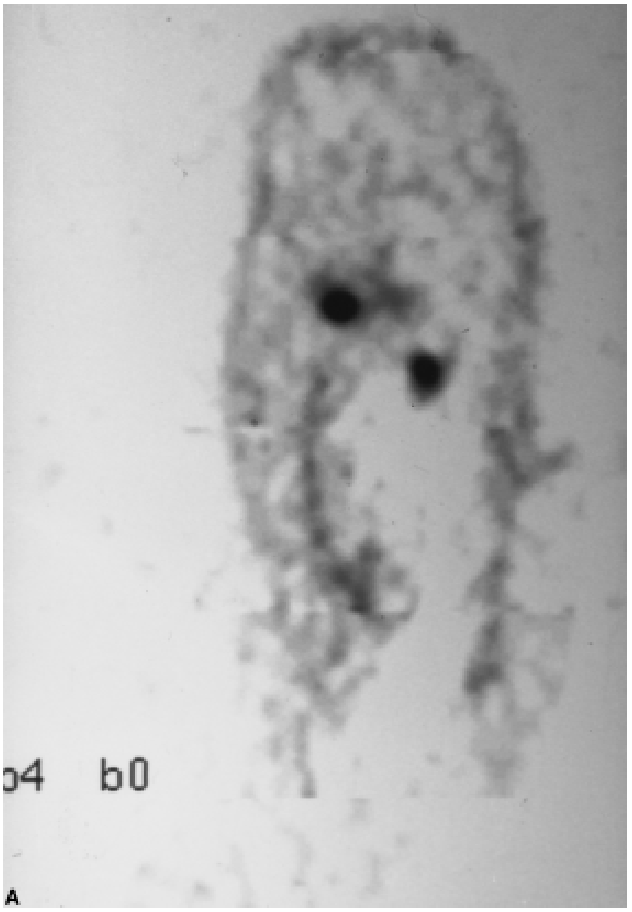


Fig. 1. Patient No. 8. **a:** Multiple subcortical metastatic melanoma deposits in 1.2 cm right inguinal lymph node. **b:** As demonstrated by preoperative fluorodeoxyglucose positron emission tomography scan. A preoperative MRI of this area was normal.

son of FDG-PET scan results to the ''gold standard'' of histologic analysis of mapped sentinel nodes (or complete lymphadenectomy specimens) of all nodal basins demonstrated to be at risk of occult metastatic disease would be necessary to determine the true sensitivity and specificity of FDG-PET for detection of subclinical lymph node metastases.

This report evaluates FDG-PET for detection of regional melanoma metastases in nonpalpable lymph node basins by comparison to histologic analysis of complete



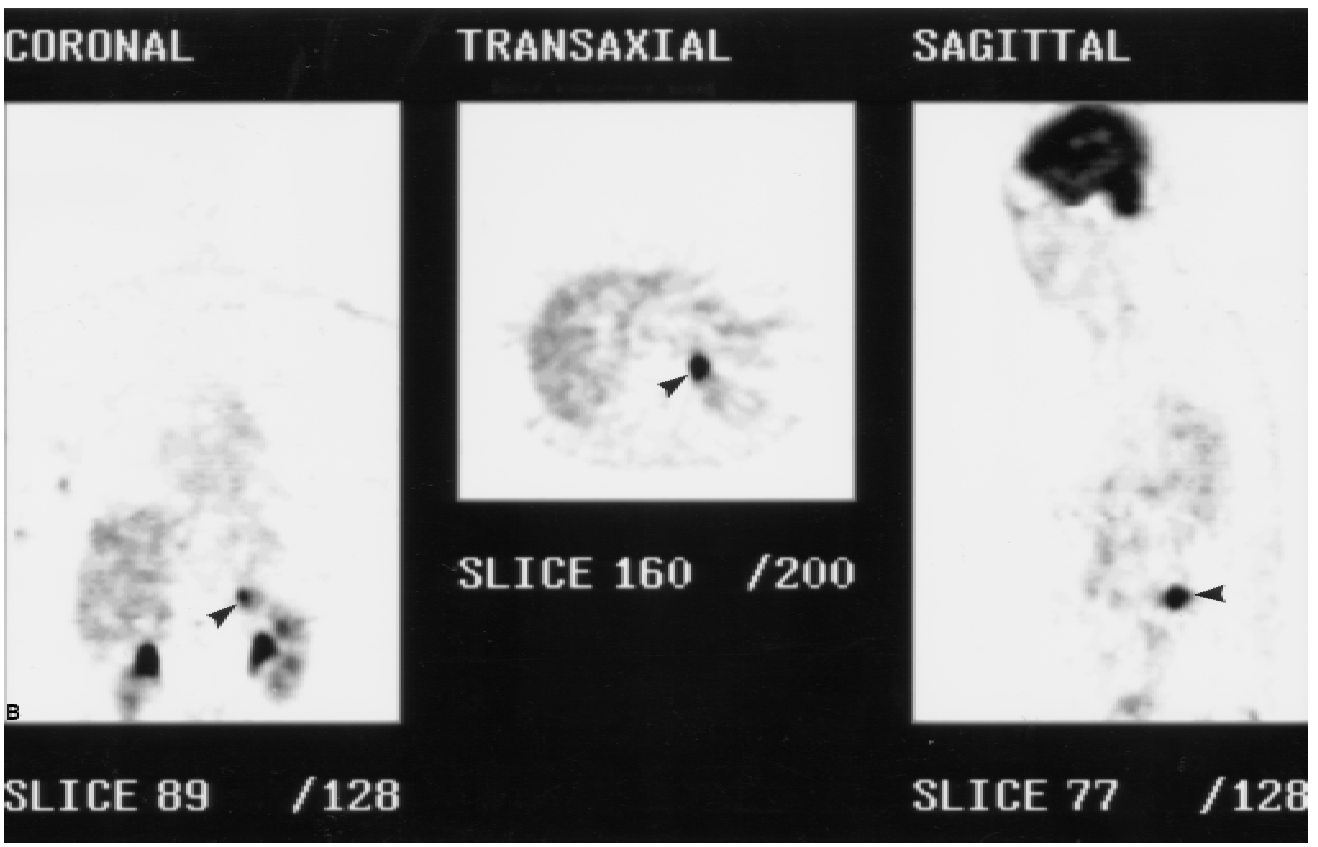


Fig. 2. **a:** Patient No. 6. Parasagittal fluorodeoxyglucose positron emission tomography image demonstrates two nonpalpable axillary nodules in previously biopsied basin. Scan was performed 3 weeks after excisional biopsy of clinically solitary cutaneous recurrence in axillary dissection scar. Repeat axillary dissection revealed two of three nodes (6-mm and 10-mm) contained melanoma. **b:** Patient No. 6. Increased fluorodeoxyglucose uptake in left adrenal metastasis; initially missed by CT scan, but subsequently confirmed by CT-guided fine-needle biopsy.

regional lymphadenectomy specimens. Clinical examination is known to be an insensitive test for regional lymph node metastases. ''Nonpalpable'' is an inherently nonquantitative clinical descriptive term that varies according to the expertise of the examiner, the body habitus of the patient, and the status of the lymph node basin. Some lymph nodes are usually palpable to the experienced examiner. Subjective differences in interpretation of normal nodes, reactive adenopathy, and adenopathy suspicious for malignancy are difficult to quantify.

Other limitations of this series are apparent. FDG-PET was sensitive for detection of regional melanoma metastases in the study population. It must be emphasized this was a heterogeneous group of patients selected for study because of anticipated moderate to high risk of nonpalpable residual or subclinical metastases. Each of the seven true-positive FDG-PET patients in this series had previously proven stage III melanoma, three by prior excisional biopsy of solitary enlarged nodes in the resected lymph node basin. In these patients, FDG-PET scan imaged *residual* disease. By strict definition, these patients did not have truly occult disease. The other three true positive patients had intransit metastatic disease and one developed palpable adenopathy shortly after FDG-PET imaging. These facts, along with the high regional lymph node tumor burden found at surgery and high prevalence of lymph node metastases (50%), confirm a high regional disease burden in the patients with true-positive PET scans. This regional disease burden is possibly overestimated because of the rapid interval development of bulky adenopathy in one patient, but was substantially higher than would be expected in clinical stage I primary melanoma patients subjected to sentinel node biopsy analysis. Therefore, results of this study should not be extrapolated to AJCC stage I and II clinical scenarios.

This series also suffers from lack of consistent lymphatic mapping. One patient underwent lymphatic mapping of a truncal melanoma. Five patients had regional basins anatomically ascertained with reasonable certainty because of the anatomic location of the primary recurrence. The remaining five patients each had regional recurrences of truncal melanomas, and could not undergo lymphatic mapping to identify all basins at risk for metastases because of prior wide excision. Each underwent lymphadenectomy for biopsy-proven nonpalpable residual disease. In these patients, other basins at risk for harboring subclinical disease may not have been interrogated. However, at a mean follow-up of 11 months, no patient has developed a recurrence in a lymph node basin negative by FDG-PET imaging.

There were no false-positive regional FDG-PET scans in this series. False-positive FDG-PET scans have been reported in reactive, nontumorous lymph nodes and in areas of infection [17,18]. Exclusion of patients with obvious regional lymphadenopathy from this study accounts for the excellent specificity of FDG-PET. This is a clinically relevant exclusion because melanoma patients with obvious lymphadenopathy already have an indication for biopsy or surgery.

Four of the seven true-positive FDG-PET scans in this series were in basins that had been previously biopsied. FDG-PET theoretically could have identified a nearby healing incision or reactive adenopathy, rather than melanoma metastases. This is unlikely, because the nodes were nonpalpable, no infection was present, and in each positive basin the FDG-PET scans identified multiple areas of increased uptake deep to the skin. Recent surgical sites distant to the lymph node basins in several patients did not show increased uptake.

PET is a physiologic imaging modality. FDG-PET scans have a spatial resolution of about 5 mm [19]. Because melanoma tumors have a very high uptake ratio, smaller foci of disease may be visible. The minimum melanoma tumor burden in lymph nodes necessary for detection by FDG-PEt is unknown. Although not demonstrated in this series, very small foci of disease could be missed. FDG-PET scanning is unlikely to be as sensitive as histologic analysis for detection of truly microscopic metastatic foci. A false-negative regional FDG-PET scan has occurred at this institution in a melanoma patient with a microscopic metastasis in a lymph node. If such microscopic foci were the sole site of metastatic disease, false-negative scans might be clinically important.

FDG-PET scans in this prospective series were highly sensitive and specific for detection of melanoma metastases in palpably nonsuspicious regional nodal basins. This is clinically relevant, because this group of patients may be subjected to prophylactic lymph node dissections. Since increased FDG uptake is suggestive of malignancy, lymphoscintigraphy and diagnostic surgical interrogation may be avoided in some clinical settings. In addition to being more sensitive and specific than CT scans for staging of metastatic melanoma [18,19], another advantage of FDG-PET includes rapid whole body imaging. This additional staging information could prevent some patients found to have distant metastatic disease from undergoing unnecessary procedures. These characteristics make FDG-PET potentially cost-effective as a tool for melanoma staging.

Several disadvantages of FDG-PET scans deserve mention. FDG uptake is higher in brain, urinary tract, liver, mediastinum, and in exercised skeletal muscle [18,19], possibly making these areas more difficult to image with the same accuracy as peripheral lymph node basins. Because of its limited anatomical resolution, FDG-PET findings must be correlated with other imaging modalities to localize biopsy confirmation of deep metastatic lesions [19]. FDG-PET may not have suffi-

cient anatomical resolution to predict accurately the number or size of lymph nodes containing melanoma.

CONCLUSION

This study suggests that an area of increased uptake in a nonpalpable regional lymph node basin in patients with melanoma is indicative of subclinical or residual metastatic disease. A positive scan may be used to guide selection for lymphadenectomy in this group of patients. FDG-PET can identify metastatic melanoma within normal sized lymph nodes, but the minimal tumor burden necessary for detection is unknown. An increasing role may be indicated for FDG-PET in melanoma staging. FDG-PET scans deserve further study in patient populations with lower burdens of regional lymphatic metastases.

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COMMENTARY

The foregoing is a thoughtful description of a small experience with whole body positron emission tomography (PET) scanning in the detection of clinically occult disease in regional nodal basins. It is important to note that this heterogeneous patient population, with the exception of four patients, is not a group that would be considered for intraoperative lymphatic mapping with sentinel node biopsy. While it appears that PET scanning will detect small volume subclinical macroscopic disease, it is not clear that it would detect subclinical mi-

croscopic disease. Clearly, the lower limits of resolution of the technique with regard to detection of disease in nodes has not yet been determined. Thus, while the technique in this limited series was quite specific, its sensitivity has not yet been fully defined.

The techniques of PET scanning and intraoperative lymphatic mapping with sentinel node biopsy are in many ways complementary. Although preoperative lymphoscintigraphy clearly defines nodal areas at risk, including aberrantly located ''intransit nodes,'' PET scan can give some idea as to the likelihood of disease being present in those nodes, as well as indicate whether there are significant deposits of disease elsewhere in the body. In addition, with the use of a hand-held gamma probe, preoperative lymphoscintigraphy enables the operating surgeon to thoroughly sample all ''hot'' nodes in the lymph node drainage basin to ensure that the sentinel node has been excised. This is particularly important given the possibility of microscopic or submicroscopic nodal involvement not visualized by PET scan.

The findings of preoperative PET scans in patients undergoing intraoperative lymphatic mapping and sentinel node biopsy should now be evaluated, not only to discover the incidence of occult systemic disease, but also to define the lower limit of sensitivity of this technique in patients with clinically occult disease.

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